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TUMOUR NECROSIS FACTOR ALPHA AND CANCER

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ABSTRACT

Tumour necrosis factor-alpha (TNF-α, cachectin) is a member of the TNF superfamily. It was the first cytokine (cell signalling protein) to be evaluated for cancer biotherapy and its development. It is a multifunctional cytokine assuming a main job in apoptosis and cell survival just as in irritation and resistance. Still, the medical use of TNF-α is strictly limited by its noxiousness. Now, TNF-α is administered merely by locoregional drug delivery systems like isolated hepatic perfusion (IHP) and isolated limb perfusion (ILP). Meanwhile both of these processes are strictly challenging which require surgical procedure, they are chiefly used for the treatment of locally advanced sarcomas (solid tumours) like in-transit melanoma metastases, primary or metastatic unresectable liver carcinoma and limb- threatening soft tissue sarcomas. To decrease the toxicity in body of TNF-α, a number of schemes have been explored over the previous numerous decades. It has been exhibited in the detached appendage perfusion sitting that TNF-α acts synergistically with cytostatic drugs. The collaboration of TNF-α with TNF receptor 1 (TNFR-1) and TNF receptor 2 (TNFR-2) actuates a few flag transduction pathways, prompting the assorted elements of TNF-α. Tumour necrosis factor alpha produced mainly by activated macrophages, also it can be produced by many other cell types like mast cells (basophils), NK cells (natural killer cell), eosinophils (acidophils), CD4+ lymphocytes, neurons and neutrophils (polymorphs). It is involved in host defense and tissue homeostasis process. The biological effect of tumour necrosis factor alpha may ultimately beneficial or injurious to the host, depending on its period of tissue exposure, concentration and the existence of other mediators in the cellular environment. It shows antitumor activity and causes carcinoma, chronic inflammation, pulmonary, metabolic, cardiovascular, autoimmune and neurologic diseases.

KEYWORDS: Interleukin, apoptosis, carcinoma, transferrin, tumour necrosis factor alpha.

INTRODUCTION

Tumour necrosis factor superfamily and tumour necrosis factor receptor superfamily forms the equivalent ligand and receptor systems that are broadly spread in various cells and tissues. The "tumour necrosis factor" referred to a "factor" made by bacterial infections that produced tumour regression in subjective cases. TNFSF play roles in many aspects like adaptive and innate immunity, embryonic development and the maintenance of cellular homeostasis. TNF plays a main role in different events like cell differentiation, cell proliferation and cell death. **Gale A. Granger** informed a cytotoxic factor made by lymphocytes and known as lymphotoxin (in 1968) and in 1975 Lloyd J. Old informed that another cytotoxic factor produced by macrophages that named tumour necrosis factor (TNF). It was discovered that bacterial endotoxin produce and release the antitumor activity from host cells (in 1975). **Antony Cerami** and **Bruce A. Beutler** establish that cachectin (that is a hormone which initiate the cachexia) was TNF. **Cerami** and **Kevib J. Tracey** found the significant mediator role of in fatal septic shock and familiar the therapeutic effects of monoclonal anti-TNF antibodies. **TNF-α** (tumour necrosis factor alpha), a cell signalling protein involved in pathogenesis injury, infection and systemic inflammation, also known as cachexin. It is one of the cytokine that make up the acute phase reaction. It is consists of numerous homologous domain and proteins.

Structure

Tumour necrosis factor superfamily (TNFSF) members are usually homotrimers. They are type II transmembrane proteins, numerous of which can be shed from the surface of cell to act as soluble signalling molecules. The major feature of this superfamily of extracellular ligands is the trimeric TNF homology domain (THD), consist of three protomers. Every protomer is made by dual sheets consists of chains. These domains are wholly situated at the C-terminal area of the protein. On the basis of sequence and structural features in THD the TNFSF can be divided into three groups. TNFSF are 19 members that bind to 29 members of TNF receptor superfamily. These members include lymphotoxin alpha (LT-α), tumour necrosis factor alpha (TNF-α), lymphotoxin beta (LT-ß), tumour necrosis factor beta (TNF-ß), CD40 ligand (CD40LG), OX40 ligand (TNFSF4), fas ligand

(FASLG), CD27 ligand (CD70), CD30 ligand (TNFSF8), CD137 ligand (TNFSF9), TNF-related apoptosis inducing ligand (TNFSF10), receptor activator of nuclear factor kappa-B ligand (TNFSF11), TNF-related weak inducer of apoptosis (TNFSF12), proliferation inducing ligand (TNFSF13), ß-cell activating factor (TNFSF13ß), LIGHT (TNFSF14), vascular endothelial growth inhibitor (TNFSF15), TNF superfamily member 18 (TNFSF18), ectodysplasin A (ED- A). These members are well categorized functionally and structurally. In these ligands entirely have quite long loops linking the strands, resulting in a typical pyramidal outline of the trimer. All ligands are likely to bind to receptors in a similar way, the stretched out receptors settled in the ligand protomer interfaces with double significant interaction areas. The second TNFSF member, the disulfide group, be made up of BAFF, APRIL, EDA and TWEAK all of these keep distinctive disulfide connecting chain. In addition, these ligands have smaller loops, that lead to additional globular total harmonic distortion (THD) in compare to the pyramidal conventional ligands. Crystal arrangements are available for EDA, BAFF and APRIL. Binding of receptor by TNFSF group also varies from the conventional ligands. APRIL, BAFF, and TWEAK ligands interact with short, atypical TNFRSF members (TACI, BAFF-R, Fn-14 and BCMA).The third "different" ligand group holds the left behind members of the TNFSF (CD30L, GITRL, CD27L,OX40L and 4-1BBL). These ligands are categorized by very different orders, both from each other and from either the disulfide groups. Crystal arrangements have only been ascertained for the ligands GITRL and OX40L, and for receptor ligand pair OX40, OX40L.TNF-α (belongs to TNF superfamily) composed of at least 20 members. TNF-α is primarily formed as a 233 amino acid transmembrane protein that forms stable homotrimers. The soluble homotrimeric TNF-α (157 amino acid residues per monomer) can be released through proteolytic cleavage by means of a metalloprotease, the TNF-α converting enzyme. The C-terminus of it is embedded in the base structure but the N-terminus is relatively free. Therefore, the N-terminal residues do not take part in the trimer interactions and are not important for the biological activities of TNF-α. Two receptors, TNFR1, also known as tumour necrosis factor receptor superfamily member 1A (CD120a) and TNFR2, tumour necrosis factor receptor superfamily member 1B (CD120b) that binds to TNF-α. TNFR1 constitutively expressed in maximum tissues. It can be activated by both membrane-bound and trimer forms of soluble TNF-α. TNFR2, largely found in cells of the immune system, reacts only to the membrane-bound homotrimeric form of TNF-α.Increasing experimental sign has exposed that TNFR1 initiates the TNF-α's biological activities. On TNF-α binding, TNFRs form homotrimers that cause conformational variations to the receptor. A sequence of intracellular events then occur which can lead to the initiation of three major signalling cascades: nuclear factor kappa B (NK-kB) pathway, MAPK (mitogen-activated protein kinase) pathway and induction of cell death signalling.

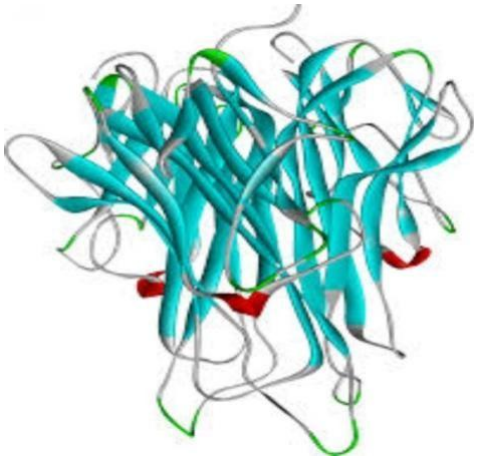

Figure 1: Structure of TNF-α.

Biological Activities of Transmembrane TNF-α

Transmembrane TNF-α (as a ligand) on the surface of cell of TNF-α producing cells binds to TNF receptors on the target cells and applies numerous biological functions that will contribute to the modulation of local inflammation in a cell to cell contact mode as well as in a cell type specific way. Expression of transmembrane TNF-α on several cell type would contribute to the physiological and pathological response in health and diseases.

Table 1: Biological activities of transmembrane TNF-α on various target cells/organs.

Target Cells/Organs	Functions
Natural Killer cell (NK cell)	Enhancement of cytotoxic activity (cytolysis or apoptosis)
Thymus cell (T cell)	GM-CSF production, expression of CD25 and HLA-DR
Bone marrow cell (B cell)	Production Ag-specific immunoglobulin, proliferation
Endothelium cell	Pro-inflammatory cytokines, induction of pro- coagulant agent,
Monocyte	Interleukin-10 (IL-10) production
Adipose tissue	Local resistance of insulin, adipocyte differentiation inhibition
Liver	Hepatitis
Heart	Concentric cardiac hypertrophy
Lungs	Interstitial inflammation

Physiology

TNF-α has several type of activities on different organ structures, usually organized with interleukin-1 (IL-1) and interleukin-6 (IL-6) that are given below:

- **On the hypothalamus:** Stimulating the hypothalamic pituitary adrenal axis by motivating the release of corticotropin releasing hormone (CRH), appetite suppression and Fever.
- **On the liver:** Stimulation of the acute phase response, leading to rise in C-reactive protein and various other mediators. TNF-α also makes insulin resistance by encouraging serine phosphorylation of insulin receptor substrate-1 (IRS-1), which ruins insulin signalling. It is a strong chemoattractant for neutrocytes and stimulates the expression of adhesion molecules on cells of endothelium.
- **On macrophages:** It stimulates the phagocytosis, production of interleukin-1 oxidants and the production of inflammatory lipid Prostaglandin E2 (PGE_2).
- **On food intake and metabolism:** Controls bitter taste observation. A low rise in concentration of TNF will induce the cardinal signs of swelling to occur: heat, redness, loss of function and pain. While high rise in concentrations of TNF cause shock like symptoms, the long contact to low concentrations of TNF can outcomes in cachexia, wasting syndrome.
- **On other tissues:** Increasing the insulin resistance, TNF phosphorylates insulin receptor serine residues, obstructing signal transduction, TNF phosphorylates the insulin receptor serine residue.

Effect of TNF-α In Treatment of Tumour

TNF-α has been illustrated to exert cytostatic or cytotoxic effects on certain animal and human cell lines. The antitumor effects of TNF-α have been shown in animal models and in human xenograft models. The antitumor activity of TNF- α in human tumor xenograft models is dependent on the method of administration of drug, with high amount of continuous doses injected directly into tumour. In breast cancer xenograft model, TNF- α was locally injected, resulted in growth inhibition of established tumours. Vascular effects are critical for TNF- antitumor activity. The necrosis detected following TNF-a remedy of isogenic mouse tumours and human tumour xenografts is due to its effects on tumour vascular endothelium like increased HLA (human leukocyte antigen) expression, TNF-α on the development of breast cancer cells might be correlated to its interfering with signal transduction from growth factor receptors. It destroys tumour blood vessels on high dose with local administration and low chronic doses of this cell signalling protein promote angiogenesis.

Table 1: Different molecular targets discovered for TNF-α founded cancer treatment.

Target	Targeting ligand
Human epidermal growth factor receptor- 2	Single chain variable fragment (scFv)
Melanoma gp240 antigen	Scfv, antibody
Transferrin receptor	Transferrin
Aminopeptidase N (CD13)	Peptide

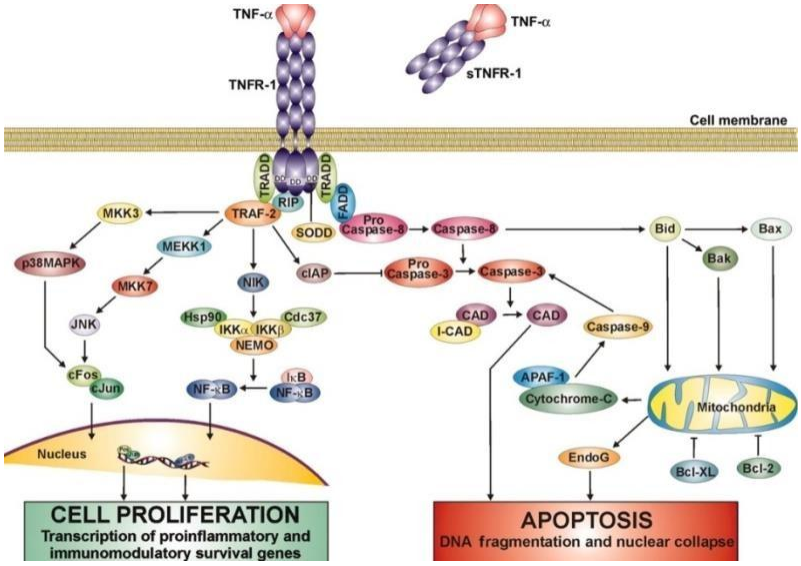

Figure 2: TNF-α in treatment of cancer.

Tumour Promoting Effects of TNF-α

TNF-α may also exert protumour effects. Some in vitro and in vivo animal models of chemical carcinogenesis recommended that TNF-α could favor cancer development. Growth stimulating actions of TNF-α have been studied in the model of skin tumour. In this study the effects of TNF-α were studied in the dual stage. Model of carcinogenesis where DMBA (9,10, dimethyl-1,2-benzanthracene) was used as tumour initiator and TPA (12-0-tetradecanoylphorbol-13-acetate) as a promotion.

It was revealed that TNF-α had no effect on initiation of tumour however influenced tumour promotion. Tumour necrosis-alpha can be produced by breast tumour cells or by cells that permeate the tumour. TAMs (Tumour associated macrophages) are important components of inflammatory permeates in neoplasm and these are derived from monocytes that are recruited basically by monocyte chemoattractant proteins (CCL2, CCL8, CCL7). TAMs have a dual role in neoplasms: they may destroy neoplastic cells following stimulation by interleukin-2, interferon and interleukin-12, however they also produce a various number of TNF-α mediators that potentiate tumour development (angiogenic and lymphangiogenic growth factors, cytokines and proteases). A main TAM derived inflammatory cytokine shown to be greatly expressed in breast cancer is TNF-α.

A number of studies proposed that the prolonged expression of TNFa in breast tumours essentially supported tumour development. The numeral cells expressing TNF-a in inflammatory breast tumour was found to be linked with growing tumour grade and node participation and TAM-derived TNF-α expression was recommended to play a key role in the metastatic behavior of breast cancer.

TNF-α may force tumor progression and development by various routes. It may produce expression of matrix metalloproteinases (MMP), endothelial adhesion molecules, promalignant chemokines and several angiogenic mediators. TNF-α cause DNA destruction reactive oxygen intermediates, whose complete effects donate to tumorigenesis.

Cytokines, inflammatory cells and chemokines are essential reasons in tumour microenvironment and their connections form a difficult web that might crucially affect tumour progress. Tumour cells express chemokines (CCL2 and CCL5). These chemoattractant proteins produce monocyte movement to tumour sites. The resulting TAMs express numerous protumour intermediaries like TNF-α. The expression of chemokine ligand 5 (RANTES) was shown to be raised by TNF-α single-handedly or in synergism with IFN-8 (interferon-8) in diverse cells of breast cancer. Also macrophages, TNF-α could be articulated by breast cancer cells and stromal cells as well. Monocytes and additional peripheral blood leukocytes need the manufacture of MMP to travel through basement layers. Gelatinases MMP-2 (matrix metallopeptidase-2) and MMP- 9 (matrix metallopeptidase-9) are specially essential in this procedure, as they are skilled of demeaning basement membrane proteins. The production of these proteases is important for tumour invasion as well. It is effective stimulator of MMP-9 production in monocytes. TNF-α contains the ability to stimulate the expression of endothelial adhesion molecules. In breast carcinoma it might control thymidine phosphorylase that is a significant angiogenic enzyme in tumour epithelial layer. TNF-α might contribute to tumour development by improving the manufacture of reactive oxygen species (ROS) by cancerous cells. Reactive oxygen species induce mutagenic variations that could outcome in improved DNA destruction and they prevent DNA repair enzymes. As a final point, TNF-α stimulates transcription factor NF-kB.

This cytokine is one of the intermediaries of breast tumour that is related to bone metastasis activity. TNF-α considered a major mediator of cancer anorexia-cachexia syndrome. Higher concentration of TNF-α in patients with stage IV breast cancer who have developed weight loss compared to patients with the same stage who had not developed weight loss. Tumour necrosis alpha is also a good regulator of oestrogen production in bordering tissues together with usual and cancerous breast cells. It raises the actions of enzymes that are involved in oestrogen production: estradiol-17ß- hydroxysteroid dehydrogenase, estrone sulphate and aromatase.

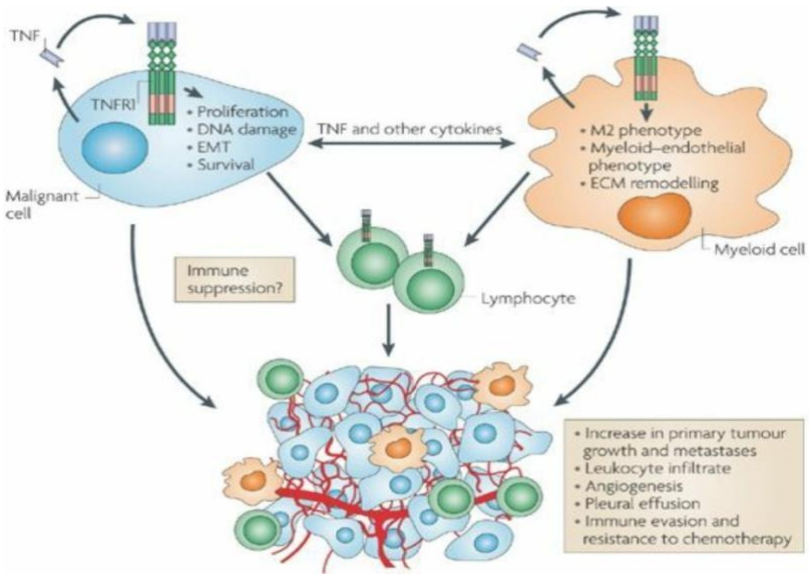

Figure 3: TNF causing cancer.

TNF-α Inhibitor

A TNF-α inhibitor is a pharmaceutical medicine that suppresses the body natural reaction of TNF-α, that is fragment of the inflammatory response. TNF-α is involved in immune-mediated and autoimmune disorders like inflammatory bowel disease, rheumatoid arthritis, refractory asthma and psoriasis. Therefore TNF-α inhibitors may be used in treatment of above diseases. The significant side effects of TNF-α inhibitors include systemic side effects, lymphomas, demyelinating disease, infections, congestive heart failure, induction of auto-antibodies, a lupus-like syndrome, and injection site reactions. Examples: infliximab (Remicade), golimumab (Simponi), adalimumab (Humira), infliximab (Remicade), certolizumab pegol (Cimzia), etanercept (Enbrel), Thalidomide (Immunoprin) and its products, pomalidomide (Imnovid), lenalidomide (Revlimid). pentoxifylline) and bupropion.

Anti-TNF-α treatment has shown only special effects in cancer treatment. Therapy renal cell carcinoma with infliximab resulted in elongated disease stabilization in some patients. Etanercept was tested for giving patients with ovarian carcinoma and breast carcinoma displaying elongated disease stabilization in some patients by down regulation of CCL-2 and IL-6.

CONCLUSION

TNF-α are part of the complex contacts between tumour and its microenvironment that can intensely affect tumour actions. On low doses TNF-α stimulate biological functions, medium doses cause stronger stimulation, high doses inhibit the stimulation, and very high doses lead to paralysis of biological functions and structures.

TNF-α is a type of cytokine that contains protumor and antitumor actions. The TNF-α inhibitor (medicines that supress the physiological responses to TNF) like Ingliximab (remicade) and gemcitabine (gemzar) used for the treament of patient with advanced pancreatic carcinoma. The multifunctional activities of TNF-α may result in an progressively changed the use of this cytokine.

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